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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,854	11/08/2005	Ilaria Adamo	2352.0010001/SRL/KPQ	5237

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EXAMINER	
CRANE, LAWRENCE E	
ART UNIT	PAPER NUMBER
1623	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,854	ADAMO ET AL.	
	Examiner	Art Unit	
	LAWRENCE E. CRANE	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *January 31, 2005 (preliminary amendment)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 14-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/27/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The Abstract of the Disclosure is objected to because is does not meet the requirement of the MPEP for US application. Correction is required. See MPEP 608.01(b).

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts, compounds or compositions, the general nature of the compound or composition should be given as well as its use, e.g., "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. Complete revision of the content of the abstract is required on a separate sheet.

Applicant is respectfully requested to amend the abstract because the Abstract is not in US format.

The instant disclosure fails to include "Cross-References to Related Applications." See 37 C.F.R. §1.78 and MPEP at §201.11. Applicant is respectfully requested to include the requested information as the first paragraph of the disclosure.

Claim **13** has been cancelled, claims **5, 6, and 10-12**have been amended, the disclosure has been amended at page 1, and new claims **15-23** have been added as per the preliminary amendment filed January 31, 2005. One Information Disclosure Statement (**1** IDS) filed October 27, 2005 has been received with all cited non-US Patent references and made of record.

Claims **1-12 and 14-23** remain in the case.

Note to applicant: when a rejection refers to a claim **X** at line y, the line number "y" is determined from the claim as previously submitted by applicant in the most recent response including ~~lines deleted by line through~~.

Claims **1-12 and 14-23** are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabled only for the solution-based synthesis of oligonucleotides and the phosphorothioate analogues thereof via either phosphoramidite coupling chemistry or H-

phosphonate coupling chemistry wherein reagents are frequently present on ther surface of solid support carriers, does not reasonably provide enablement for the synthesis of oligonucleotides and the phosphorothioate analogues thereof via any process wherein the oligonucleotide or analogue thereof is attached to a solid support. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims is excessive because of the presence of incompletely-defined terminology that does not clearly distinguish between the presence of support-bound oligonucleotide and non-support bound oligonucleotides; e.g. in claim **1** at lines 9-10 the terms "3'-protected nucleotide" and "3'-protected oligonucleotide" are to further defined to exclude a -- solid-support attachment -- as the basis for the protection. In addition, the claims are broadly drafted to include many nucleotide analogues but the instant specific embodiments appear to be restricted to naturally occurring DNA and RNA monomers. Examiner also notes that in Example 55, directed to making a protected C-T-dG trimer, doe snot specify the chemical identity of the "C" monomer in the synthesis, thereby rendering the synthetic protocol incomplete and suggesting that at least one portion of the disclosure is missing critical information necessary to execute one exemplification of the claimed process.

B. The nature of the invention is directed to the synthesis of oligonucleotides and phosphoramidite analogues thereof via either phosphoramidite coupling chemistry or H-phosphonate coupling chemistry but conducted with the growing oligonucleotide precursors in solution with reagents and activators attached to solid supports.

C. The state of the prior art and the disclosures therein may be interpreted to suggest that the instant claims as presently in the case may be found to be directed to either the above described process or to classical solid support-based oligonucleotide syntheses as described by Caruthers et al. and Frochler et al.

D. The level of one of ordinary skill would be expected to be knowledgeable in the area of oligonucleotide synthesis.

E. The level of predictability in the art appears to be fairly high as claimed process may be seen as little more than an application of classical oligonucleotide synthesis process chemistry with the reagents attached to solid supports and the growing oligonucleotide present in solution.

F. The amount of direction provided by the inventor is extensive with 56 examples provided.

G. The existence of working examples is discussed in the previous paragraph.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be excessive because of confusion about the scope of the claimed subject matter and whether applicant is claiming both the above described process wherein the growing oligonucleotide is in solution and a solid state process similar to the processes well described in the prior art cited on the PTO-892. . .

Claims **1-4, 11, 12 and 14** are objected to because of the following informalities:

In claim **1** at line 8, the term "methylen" is a misspelling of -- methylene --. See also claims **2-4 and 14** wherein the same error reoccurs.

In claim **1** at line 14, the term "proctection" is a misspelling of the term -- protection --. See also claims **2, 3 and 12** wherein the same error reoccurs.

In claim **1** at line 24, there is inappropriate terminal punctuation at the end of the noted line.

In claim **11** at line 3, the term "an cationic" is grammatically incorrect. Did applicant intend the noted term to read -- a cationic --?

Appropriate correction is required.

Claims **1-12 and 14-23** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **1** the claimed process is described with generic and funcitonal terminology to frequently that is impossible to determine the metes and bounds of what is being claimed. For example, at lines 9-10 the terms "3'-protected nucleotide" and "3'-protected oligonucleotide" fail to provide the details necessary to determine what the chemistry being claimed really is. Similarly at lines 13-15, the process step "b)" is described functionally with the term "a nucleotide derivative having a 5'-protection group," a chemical reagent that is not adequately defined by the term "a solid supported activator," and the nature of the product as having "a P(III)-intermediate bond," terms that suggest a hide-the-ball strategy that has almost entirely obscured the nature of the invention. A clarifying amendment is respectfully requested for this claim and for the remaining claims many of which suffer from the same or a similar problems.

In claim **1** at lines 18-21, the terms "a solid supported capping agent" and "a solid supported oxidizing reagent" are entirely functional and therefore meaningless. Examiner respectfully suggests added specific definitions for each noted term to the noted claim and to other independent claims as necessary. See also claim **1** at lines 22-25 wherein neither of the term "solid supported agent" and "a solid supported scavenger" provide even a brief clue concerning the chemical process being alluded to by these entirely functional terms. See also claims **3 and 14** wherein similar problems reoccur.

In claim **6** at line 4, the term "pyridinium" is incomplete. Did applicant intend the term to read -- pyridinium salt?" See also claim **12** at line 5, claim **16** at line 3, and claim **22** at line 4 wherein the same or a similar error appears.

In claim **6** at line 8, a Markush preamble should be inserted before the term "carboxylic acid" in order to make the end of the claim a proper Markush group.

In claim **7** at line 3, the term "solid supported periodates" should be amended to read -- a solid supported periodate -- and following terms should be checked for similar grammatical errors. See also claims **10, 17 and 20** wherein similar grammatical errors reoccur.

Claim **8** lacks proper antecedent basis because claim **1** does not refer to "sulfurization." Examiner respectfully suggests addition of sulfurization as an option in claim **1**. See also claim **18** wherein the same error reoccurs.

In claim **12** at line 2, the term "in the F-form" is not defined in the claim. Clarification is respectfully requested. See also claim **22** at line 2 wherein the same error reoccurs.

In claim **23** is an incomplete description of a chemical, process step because the chemical formula at line 4 is incorrect (tetrathionite ion is "$S_4O_6^=$.) and the chemical formula bridging lines 4 and 5 is an ion, not a compound and therefore not correctly named or alternatives lines 4-5 should be amend to provide a complete chemical name and a complete defined formula of the salt intended. .

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **1-12 and 14-23** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Caruthers (I)** (PTO-892 ref. **R**) in view of **Caruthers (II)** (PTO-892 ref. **T**) and **Zon and Stec** (PTO-892 ref. **S**) and further in view of **Patil et al.** (PTO-1449 ref. **NPL6**) and **Sanghvi et al. '922** (PTO-1449 ref. **FP2**: **WO99/62922**).

The instant claims are directed to processes for making either an olignucleotide of an oligonucleotide with one or more phosphorothioate linkages wherein the growing oligonucleotide precursors is in solution and the reagents effecting changes to the precursor molecules are attached to or adsorbed on solid supports, OR the precursor molecules are also attached to solid supports.

Caruthers (I) (PTO-892 ref. **R**) discloses at pages 48, 48 and 51 (Figures 1, 2 and 3) that oligonucleotides can be synthesized with either phosphoramidite or H-phosphonate coupling chemistry with the growing oligonucleotide remaining in solution. At page 59 this reference discloses that there are numerous nitrogen heterocycles that mey be used to promote the

coupling reaction and at page 80 (Figure 11) illustrates that P(III) linkages can be oxidized to produce phosphorothioates with numerous different sulfurization reagents. This reference also discloses that both phosphoramidite-based and H-phosphonate-based processes are effective when the precursors are attached to a solid support.

Caruthers (I) does not expressly disclose that solid state attached oir adsorbed reagents can be effective substitutes for similar reagents in solution to effect the coupling and oxidation process steps in oligonucleotide syththeses.

Caruthers (II) also discloses at page 15 at Figure 1.4 that oligonucleotide dimers with a P(III) linkage can be synthesized in solution and precursors in the synthesis of phosphorothioates. This reference also discloses that both phosphoramidite-based processes are effective when the precursors are attached to a solid support.

Zon and Stec at pages 97-100 disclose several different routes wherein oligonucletide precursors with P(III) linkages can be converted into phosphorothioates in the presence of numerous sulfurization reagents.

Patil et al. (PTO-1449 ref. **NPL6)** discloses that a solid support attached sulfonic acid polymer is effective in the detritylation of a nucleotide with a 5'-trityl protecting group.

Sanghvi et al. '922 (PTO-1449 ref. **FP2**: **WO99/62922)** discloses at page 4 beginning at line 9 that the prior art includes reports of numerous "activators" with utility in promoting the phosphoramidite coupling reaction.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to engage in optimization of the prior art disclosures of **Caruther (I)** and **Caruthers (II)** of solution-based oligonucleotide syntheses by the substitution of polymeric reagents based on the teachings of **Patil et al.** Alternatively, if the instant claims are actually directed to solid-state oligonucleotide syntheses, then the disclosures of the **Caruthers** references, plus the disclosures of **Zon and Stec**, directed to solid-state oligonucleotide syntheses, could also be subject to optimization in view of the **Patil et al.** reference. In addition, the **Patil et al.** reference may be interpreted to be a teaching that permits the ordinary practitioner to incorporate the teachings of **Sanghvi et al. '922** *in re* activators to attempt optimization of the coupling steps in either liquid phase or solid state process by modification

of a polymer by addition of substituent groups capable of acting as activators when applied in solution as monomers in classical solid-state oligonucleotide syntheses.

One having ordinary skill in the art would have been motivated to combine these references because all of the references are directed to one or more aspects of oligonucleotide synthesis process steps including coupling, either oxidation or sulfurization, and deprotection.

Therefore, the instant claimed processes directed to making oligonucleotides or oligonucleotide phosphorothioate analogues would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. S. Anna Jiang, can be reached at **571-272-0627**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status Information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see < http://pair-direct.uspto.gov >. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

LECrane:lec
10/01/2008

/Lawrence E. Crane/

Examiner, Art Unit 1623

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